Genomics Education Programme

NHS Health Education England

Lynch Syndrome
(Hereditary non-polyposis colorectal cancer)

Key facts

- Lynch syndrome is a cancer predisposition syndrome causing individuals to have a high risk of colorectal cancer. Women also have a high risk of endometrial cancer and an increased probability of developing ovarian cancer.
- It occurs due to the inheritance of an alteration in one of the mismatch repair genes (*MLH1, MSH2, MSH6,* and *PMS2*).
- Immunohistochemistry staining of the tumour tissue for mismatch repair proteins can help to identify tumours occurring due to Lynch syndrome (due to abnormal staining), facilitating diagnosis of Lynch syndrome in individuals and families.
- Lynch syndrome tumours also show microsatellite instability (MSI), a characteristic of defective mismatch repair. Testing cancer tissue for MSI can be a useful in diagnosing the condition.
- Frequent colonoscopy screening (usually every two years) improves survival by identifying colorectal cancers at an early stage and by identifying and removing adenomas which may otherwise grow and develop into invasive cancers.

Clinical features

- A high probability of developing colorectal cancer (50%-80%), often at younger ages than usual.
- An increased probability of developing endometrial (30%-60%) and ovarian cancer (10%) in women.
- A slight increase in risk for other tumours including kidney, stomach, urinary tract and pancreatic cancer.
- Polyps (adenomas) can and do develop, but not usually in high numbers (as distinct from polyposis syndromes).
- The following are clinical clues that Lynch syndrome may be present in a family:
    - Several family members with colorectal cancer (usually 3 or more), usually over more than one generation.
    - Several relatives with a combination of colorectal, endometrial and ovarian cancer.
    - Colorectal cancer occurring at a younger age than usual (often below the age of 50).
    - An individual developing more than one primary colorectal cancer or a combination of colorectal, endometrial and ovarian cancer.

Diagnosis

- Careful assessment of family history is important to determine the likelihood of Lynch syndrome and to consider other bowel cancer predisposition syndromes (such as FAP and MYH polyposis).
- Diagnosis is usually through genetic testing for alterations in the mismatch repair genes.
- Testing through immunohistochemistry or microsatellite instability testing may be carried out initially to determine whether there is impaired mismatch repair function in a tumour, particularly where there is limited family history. Impaired mismatch repair is suggestive of Lynch syndrome but also occurs in 15%-20% of sporadic tumours so is not unique to Lynch syndrome.

Genetic basis

- Lynch syndrome results from an alteration in one of the mismatch repair genes: *MLH1*, *MSH2*, *MSH6* or *PMS2*.
- The risks of developing particular cancers and penetrance of Lynch syndrome are variable. There is some variability between the genes involved. *MSH6* alterations appear to confer a higher probability of developing endometrial and ovarian cancer, but a lower probability of developing bowel cancer. The overall probabilities of developing cancer are generally considered lower for *PMS2* alterations.
- These genes have an important role in the repair of DNA damage (base mismatches). Defects in mismatch repair lead to the accumulation of DNA damage across the genome, causing cancers to develop and progress.
- Lynch syndrome is inherited in an autosomal dominant manner: an alteration in one copy of a gene pair is sufficient to convey an increased risk of cancer. Each child of an individual with Lynch syndrome has a 1-in-2 (50%) chance of inheriting the gene alteration and also having Lynch syndrome.
- Individuals who have inherited alterations in both copies of a mismatch repair gene (and are homozygous or compound heterozygous for alterations in a mismatch repair gene) have been described, but these occurrences are rare. These individuals have a distinct presentation with a high probability of developing colorectal cancer, leukaemia, brain tumours and other cancers developing in childhood. This usually occurs because both parents have Lynch syndrome.

Clinical management

- Regular colonoscopy (usually every two years) from age 25 onwards for those with Lynch syndrome or at 50% risk (if testing not possible or declined) enables cancers to be detected at an early stage and adenomas to be identified and removed.
- Continued surveillance of remaining bowel tissue is important for those who have developed colorectal cancer, as there is an increased chance of further cancers.
- It is important that women are aware of the symptoms of endometrial and ovarian cancer and seek advice if they experience unusual vaginal bleeding or discharge or abdominal pain, discomfort or bloating.
- In some centres, endometrial screening is offered by ultrasound and pipelle biopsy and ovarian screening by transvaginal ultrasound and serial CA125 measurement but the evidence of benefit of this is limited. Hysterectomy and salpingo-oophorectomy is an option for women who wish to reduce the risk of these gynaecological cancers.
- There is mounting evidence that low dose, enteric-coated aspirin for 4 years or more can reduce the risk of bowel cancer for those with Lynch syndrome and may be recommended for those without contraindications.

Genetic testing

- Laboratory analysis of *MLH1, MSH2, MSH6* and *PMS2* through a combination of sequencing and tests to look for larger deletions is widely available.
- Initial testing in an affected family member is preferable to determine whether the cancers are related to Lynch syndrome and to identify the specific family mutation.
- Presymptomatic genetic testing can then be offered to at-risk relatives to identify those who carry the alteration and would benefit from screening.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.